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HEALTH POLICY ANALYSIS

Pharmaceutical Priority Setting and the Use of Health Economic Evaluations: A Systematic Literature Review

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ABSTRACT

Objectives: To investigate which factors and criteria are used in priority setting of pharmaceuticals, in what contexts health economic evaluations are used, and barriers to the use of health economic evaluations at micro, meso, and macro health-care levels. **Methods:** The search for empirical articles was based on the MeSH index (Medical Substance Heading), including the search terms “economic evaluation,” “cost-effectiveness analysis,” “cost-utility analysis,” “cost-benefit analysis,” “pharmacoeconomic,” AND “drug cost(s),” AND “eligibility determination,” AND “decision-making,” AND “rationing,” AND formulary. The following databases were searched: PubMed, EconLit, Cochrane, Web of Science, CINAHL, and PsycINFO. More than 3100 studies were identified, 31 of which were included in this review. **Results:** The use of health economic evaluations at all three health-care levels was investigated in three countries (United States [US], United Kingdom [UK], and Sweden). Postal and telephone survey methods dominated ($n = 17$) followed by in-

terviews ($n = 13$), document analysis ($n = 10$), and observations of group deliberations ($n = 9$). The cost-effectiveness criterion was most important at the macro level. A number of contextual uses of health economic evaluations were identified, including importantly the legitimizing of decisions, structuring the priority-setting process, and requesting additional budgets to finance expensive pharmaceuticals. **Conclusion:** Factors that seem to support the increased use of health economic evaluations are well-developed frameworks for evaluations, the presence of health economic skills, and an explicit priority-setting process. Differences in how economic evaluations are used at macro, meso, and micro levels are attributed to differences in the preconditions at each level.

Keywords: economic evaluation, literature review, pharmaceutical, priority setting.

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Introduction

A (formal) health economic evaluation can be described as an investment appraisal related to health care or health, in which both costs and consequences (e.g., utility) are compared for two or more alternatives. Despite the growing number of health economic evaluations, little is known about how these studies are used in medical decision making. For example, are health economic evaluations even used, and if so, by whom and when? A previous literature review of the use of health economic evaluations in general [1] suggested that health economic evaluations are used at all three (macro, meso, and micro) health-care levels. Macro-level decision makers are those with a national or regional health-care perspective and who coordinate the use of health-care resources outside health-care organizations. They are therefore responsible for the availability of effective and affordable health care intended for the whole population. Meso-level decision makers are involved in decisions that are oriented inside health-care organizations, for example, formulary decisions or the development of local clinical guidelines. The third level is the micro level, which covers the activities of individual prescribers at the patient level.

The proportion of all cost-utility analyses focusing on pharmaceuticals increased from 33.6% for the period 1990 to 1995 to 47.3% for the period 2001 to 2006 [2]. Although the methods that govern the application of economic evaluations can be equally applied to pharmaceuticals and medical devices, there is currently asymmetry in the way in which pharmaceuticals and devices are regulated [3]. With a few exceptions, most of the literature on the use of health economic evaluations was concerned with health economic evaluations in general [1,4–8].

This means that there is a lack of reviews considering the use of health economic evaluations in the pharmaceutical context; that is, who are the decision makers at the macro, meso, and micro levels and which factors or criteria do they use, in which situations and contexts are these factors/criteria used, and what are the barriers to their use. This leads to the objectives that this literature review intended to investigate: 1) which factors or criteria are used in priority setting of pharmaceuticals, 2) in what contexts are health economic evaluations used (or not used if specified), and 3) what are the barriers to use of health economic evaluations at micro, meso, and macro health-care levels?

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Methods

The methods used were based on the methodology proposed by the Centre for Reviews and Dissemination at the British National Institute for Health Research, York University [9].

Review of previously published systematic literature reviews

This review began with a search for previously conducted systematic literature reviews on the subject of interest found in the PubMed, Cochrane Database of Systematic Reviews, CINAHL, and PsycINFO databases. The titles and abstracts of the results of these searches were also browsed for potentially relevant articles. Hard copies of potentially relevant reports were obtained. Articles were to be included in this review if they satisfied the following criteria:

- Study design: Based on empirical data and using any of the following qualitative and/or quantitative methods,
- Population in included studies in review: decision makers at macro, meso, or micro health-care level,
- Study objectives: 1) assessments or description of pharmaceutical-related priority-setting processes (i.e., how decisions are made and based on what grounds; 2) assessments of barriers to the use of economic evaluations; or 3) assessments of the contextual use of health economic evaluations in pharmaceutical priority setting.

Although the author was responsible for all data extractions, a senior researcher was consulted to audit the search and decide on borderline studies. Disagreements were resolved by discussion, and, if needed, a third researcher was available for the final decision making. All decisions were recorded, and all excluded reviews were assessed for relevance to other sections of this review. The quality and findings of the included reviews were reported textually. The author has not conducted a quantitative meta-analysis, but instead reported in text (qualitatively) the important results from various studies.

In total, four systematic reviews were identified [10–13]. Three of these reviews failed to define what they meant by economic information and/or cost-effectiveness [10–12], and in one [13], cost-effectiveness was not the main focus of the review, resulting in continued uncertainty regarding the use of formal health economic evaluations. No review covered all three health-care levels, and none included the micro level. Three of the four analyses investigated the use of factors and/or criteria used in decision making and/or the barriers to use of economic evaluations [10–12]. The only review to consider the contextual nature of the factors or criteria used did not have health economic evaluations as a primary focus [13].

Review of empirical studies of pharmaceutical priority setting

The search for empirical articles took its departure from the MeSH index (Medical Substance Heading). The following search terms were used: “economic evaluation,” “cost-effectiveness analysis,” “cost-utility analysis,” “cost-benefit analysis,” “pharmacoeconomic” in combination with either of the following search terms “drug cost(s),” “eligibility determination,” “decision-making,” “rationing,” and “formulary.” Consequently, the search terms were used in pairs following a predefined pattern. The final electronic search strategy was developed through a process of refining and revising search terms with the aim of maximizing the number relevant articles retrieved. The following databases were searched; PubMed, EconLit, Cochrane, Web of Science, CINAHL, and PsycINFO. In addition, a number of peer-reviewed journals such as *Social Science of Medicine*, *Health Policy*, *Applied Health Economics*, *European Journal of Health Econom-*

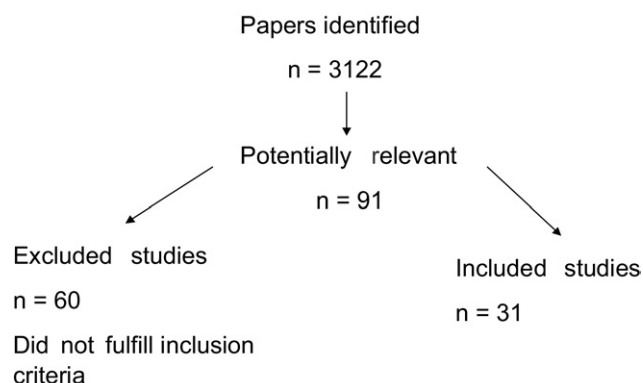


Fig. 1 – Pharmaceutical priority setting.

ics, *Journal of Health Economics*, *Health Economics*, *Value in Health*, and *Pharmacoeconomics* were searched by hand.

Studies were included that satisfied the following criteria:

1. Study design: Is the study based on empirical data and using either or any of the following qualitative and/or quantitative methods: observation of meetings, document analysis, interviews or surveys (telephone or postal)?
2. Study subjects: Macro, meso, and micro health-care decision makers;
3. Study object: Pharmaceutical priority setting;
4. Formal economic evaluations: Does the study indicate use or lack of use of cost-effectiveness analysis or any formal health economic evaluation?
5. Publication date: Published between 1990 and May 2009;
6. Language: English or Swedish.

Other materials such as editorials, letters, comments, and news were excluded from the review, as well as studies reporting on priority setting of non-pharmaceuticals. The search was restricted to articles in the English or the Swedish language, basically because of the language barrier and lack of financial funding for translational services. In addition, studies published before 1990 were excluded from the search because of the low frequency of economic evaluations published before 1990, indicating a low interest in such analyses among decision makers, as well as studies based on samples consisting entirely or partly of researchers. The search identified more than 3100 articles, which were screened for relevance. Ninety-one potentially relevant studies were selected for further investigation of relevance but only 31 of these articles showed empirically the influence of health economic evaluations in a pharmaceutical priority-setting context. Reference lists in the articles identified were also searched for more studies to include in the review. A panel of leading Swedish experts in health economics was consulted to identify studies not recorded in the databases and journals already researched. This did, however, not result in any additional studies identified (Fig. 1).

Data extraction and reporting

The data extraction form was designed by the author and tested on a sample of studies before data extraction began in collaboration with a university librarian and a senior researcher. The characteristics of the studies were described, and a synthesis of the findings of the primary studies was provided. Data were recorded about the author(s), year of the study, sample and sample size, methods, study focus, and main findings. The latter implied factor/criteria reported in studies, the contexts in which formal economic evaluations were used/not used, and barriers to the use of

economic evaluations. All retrieved studies that fulfilled the inclusion criteria were included in the analysis.

Results

Articles that evaluated the use of health economic evaluations at all three health-care levels were of specific interest in the review. Unfortunately, no such study was identified. For this reason, the findings from each level of decision makers (macro, meso, and micro) are reported individually.

Description of study populations

Macro level

The majority of studies were conducted in the US, Canada, and Australia (Table 1). The remaining articles were primarily based on results or work performed in Sweden, the UK, and France. Reimbursement agencies or formulary committee members were the most frequently sampled groups, and the most commonly used methods were interviews (8 studies) and document analysis (7 studies). Most studies, however, used both interviews and document analysis, and a few studies also observed group deliberations. Postal and telephone surveys were the least frequently used method (4 studies), and these studies were mostly published in the late 1990s or the early 2000s.

Meso level

The meso-level studies were mainly conducted in the UK and the US. Other studies were conducted in Sweden, Canada, France, Germany, The Netherlands, or France. A majority of the decision makers investigated were members of a hospital formulary committee, although the French study included pharmacists in hospitals and clinics and the Swedish study included regional county council formulary committee members (Table 2). The most commonly used method to investigate meso-level priority setting was postal and telephone surveys, followed by observation of group deliberations, interviews, and document analysis. Four of the studies used more than one research method [14–17].

Micro level

Five studies of the use of health economic evaluations at the micro level were identified in the review (Table 3). Two of these were conducted in the US, and one each in Greece, the UK, and Sweden. Although two of the US-based studies sampled only specialists [18,19], the Greek [20] and Swedish [21] studies sampled both general practitioners (GPs) and specialists. In addition, one study sampled physicians and pharmacists [22]. Postal survey was used as the method of research without exception.

Factors and criteria used in priority setting

Macro level

Most of the macro level studies found a strong ordinal approach to the way in which the criteria and analyses were considered: first clinical efficacy (sometimes defined as clinical effectiveness), safety, and then cost-effectiveness. There were, however, some differences across settings in terms of the use of the cost-effectiveness criterion. The cost-effectiveness criterion has been reported to be used more frequently in centralized European health-care systems than in more decentralized systems such as one in the US or Canada. Still, the review identifies exceptions to this observation. In the US, managed care organizations (MCOs), for instance, have also been reported to incorporate cost-effectiveness [23], whereas Grabowski and Mullins

[24] report the availability of generic substitutes (substitutability) as a prerequisite for costs to be considered at all by pharmacy benefit management (PBM) companies. In addition, a number of other less frequently used but still important criteria have been reported in the MCO setting: standards of practice, manufacturers' rebate, impact on existing formulary products, patient compliance, and available material from the US Food and Drug Administration [25]. Cancer care in Canada has been reported to also consider a number of criteria, in addition to efficacy, including magnitude of benefit, quality of evidence, alternative treatments available, cost per month, average duration of treatment, total populations affected, total yearly cost to the system (budget impact), pressure from physicians and patient groups, and historical precedent [26]. In Australia, cost to the government has also been identified as an important criterion [27]. In some countries, the criteria to be used have been legislated. In Sweden, for instance, an application for reimbursement must, according to the Swedish Act on Pharmaceutical Benefits, be evaluated on the basis of four criteria: the principles of human dignity, need and solidarity, cost-effectiveness, and marginal benefit (in order of importance).

Meso level

Similar to macro-level decision makers, meso-level decision makers favor drug efficacy and safety concerns above cost considerations. An explicit use of the formal cost-effectiveness criterion was, however, only indicated in a survey of attitudes across Swedish regional formulary committees [28]. In an observational study, Erntoft [17] found that the use of the cost-effectiveness criterion by a Swedish formulary committee varied during four phases identified in the priority-setting process. The criterion was more important in the first two phases, preparation of decision making and expert comments, and less important during the final phases, decision making and launching of the formulary and consequently not explicitly used. In hospital formulary settings, the cost-effectiveness criterion was usually defined as budget impact [29], acquisition cost or costs weighted by benefits [30], cost of the drug compared to current drug cost (alternative cost), informal cost-effectiveness [14], cost per dose or unit time [31], or immediately covered costs rather than long-term savings [32].

In addition to these frequently ranked criteria related to efficacy, safety, and cost-effectiveness, a number of more pragmatic criteria were reported; easier dosing [33], timely deliveries and length of time on the market [28], extent of drug monitoring and avoidance of the use of home infusions [30], ability of a nurse or medical attendant to administer the drug and comparative drug use in other hospitals [14], relations between decision makers and the pharmaceutical industry [34], the size of the clinical problem, the scale of the potential investment, acceptance from the budget holder [35], and pressure from clinicians [16].

Micro level

Three of the five identified postal surveys of micro-level decision makers asked about the ranking of decision criteria [20–22]. Based on these three reports, there seemed to be differences among different types of prescribing physicians (GPs or specialists) and between physicians and pharmacists. All respective groups agreed to the previously reported ordinal ranking of efficacy and other clinical issues (i.e., safety and side effects). Although physicians tended to rank patient compliance higher than cost-effectiveness [21], pharmacists were instead more interested in acquisition cost and budgetary overspend than cost-effectiveness [22].

Table 1 – Summary of macro level studies included in the review (chronological order).

Author(s) (year)	Settings	Data sources	Factors/criteria/ information	Use in context	Barriers
Hailey (1997)	PBAC (Australia), reimbursement decisions	Interviews, participant observation of deliberations	Efficacy, safety, cost-effectiveness	Reject or limit listing; health economic evaluations were claimed when the cost to the pharmaceutical benefits program was a major consideration, the treatment was not cost-effective, it was not intended for a life-threatening condition, and there were other treatments available, cost-effectiveness depended critically on subgroup analysis or the validity of assumptions made about long-term effectiveness	Efficacy superior to cost-effectiveness, limited evidence of effectiveness, pressure from the public, political judgment
Lyles et al. (1997)	51 managed care organizations in the US, formulary decisions	Telephone survey	Clinical effectiveness, safety, cost of treatment, cost-effectiveness, quality of life	N/A	N/A
Grabowski and Mullins (1997)	PBM companies in the US, formulary decisions	Interviews, documentary analysis	Efficacy, safety, substitutability (if substitutable, also cost)	N/A	Lack of studies comparing substitutable pharmaceuticals, methodological issues (e.g., transferability, discount rates, measurement of cost and benefits, industry bias)
Evans et al. (2000)	MCOs in the US, formulary decisions	Telephone survey (21 medical and 20 pharmacy directors)	Medical directors: efficacy, safety, and cost-effectiveness. Pharmacy directors: safety, efficacy, cost-effectiveness	66% of medical directors, but none of the pharmacy directors reported it as somewhat or very important in influencing the speed of approval	Reliance on assumptions; methodological issues (transferability), lack of health economic competence
Cox et al. (2000)	Managed care and PBM decision makers in the US, general concepts	Telephone interviews (n = 16)	N/A	N/A	Copay precludes the relevance of willingness to pay, limited scope with regard to local budgets, difficult to understand
Grizzle et al. (2000)	Managed care decision makers in the US	Telephone interviews		Add a drug to the formulary	Difficult to understand, irrelevant to the organization, lack of studies of relevant data
Martin et al. (2001)	Cancer Care Ontario Policy Advisory Committee (Canada), formulary decisions	Document analysis, interviews, observation of deliberations	Efficacy (magnitude of clinical benefit), quality of evidence, alternatives, cost per month, average duration of treatment, total population of patients affected, total cost to the system (yearly), pressure from physician and patient groups, historical precedent cases	Formal cost-effectiveness analysis was rarely available and not used; however, the concept was used informally	Institutions (actors) and process

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Table 1 (continued)

Author(s) (year)	Settings	Data sources	Factors/criteria/information	Use in context	Barriers
West et al. (2002)	Key provincial informants in five Canadian provinces, formulary decisions	Postal survey	Efficacy, cost per effect, cost per dose, availability of alternative therapy, cost compared to available alternatives, impact on total costs of drug benefit programs, comparative safety against alternative, cost per treatment course, effect on overall health-care costs in the province, contribution to current therapeutic armamentarium, drug compliance, patient satisfaction with drug, efficacy compared to that of placebo, pharmacology, drug interactions, chemistry	N/A	Methodological issues (transferability, missing data), industry bias
Anell (2004)	PBAC (Australia), DQTC (Canada), PI (Canada), Pharmaceutical Price Board (Finland), NICE (England and Wales), CdT (France)	Document analysis, interviews	Efficacy, clinical effectiveness	Increase in importance when a high potential budget impact; decrease in importance when the clinical need increases	Lack of health economic competence
Anell and Persson (2005)	TLV (Sweden), reimbursement decisions	Document analysis	Human dignity, need and solidarity, cost-effectiveness, marginal benefit	Increases in importance when high potential budget impact and when cost-effectiveness varies by indication and/or subgroups of patients, decrease in importance when a lack of alternative treatment therapies and severe diseases	N/A
Jansson (2007)	TLV (Sweden), reimbursement decisions	Document analysis (2002–2005), interviews	Human dignity, need and solidarity, cost-effectiveness, marginal benefit	Major rationale for rejecting or limit reimbursement, increases in importance when the demand for openness and transparency increased, decreases in importance when a lack of alternative treatment therapies and severe diseases	N/A
Bryan et al. (2007)	NICE (England and Wales), formulary decisions	Interviews, observation of deliberations, document analysis	N/A	Health economic evaluations were used as a basis for formulary decisions regarding cancer drugs. Health economic evaluations were not suitable for bipolar I disease.	Difficult to understand, methodological issues (uncertainty, consistency, assessment of benefits in very severe conditions, irreversibility), ethical considerations, presentation (graphs, disaggregation, consequences), rule of rescue, difficulties in implementing threshold values, voluntary implementation of NICE guidelines
Williams et al. (2007)	NICE (England and Wales), formulary decisions	Semistructured interviews, observation of deliberations	Clinical effectiveness, cost-effectiveness	Analytical framework, informal use of health economic evaluations	N/A

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Table 1 (continued)

Author(s) (year)	Settings	Data sources	Factors/criteria/information	Use in context	Barriers
Harris et al. (2008)	PBAC (Australia), reimbursement decisions	Document analysis (1994–2004)	Efficacy, cost-effectiveness, cost to government, resubmissions	The rate of rejection was higher for those with a cost per QALY (47%) than all submissions (37%), similar to all cost-effectiveness analyses (50%) and similar to those with a cost per LYG (40%). Those with a cost per QALY were more likely to be used as last-line therapy than other cost-effectiveness submissions and slightly more likely to have been seen before. The use of economic modeling appeared to have only a small effect on the decision to recommend coverage, with the translation from the clinical evidence to the final outcome of QALYs in the model having a small and imprecisely estimated impact.	Rule of rescue, political pressures
CdT, Commission de Transparence; DQTC, Drug Quality and Therapeutics Committee (in Ontario, Canada); MCOs, managed care organizations; N/A, not available; NICE, National Institute for Clinical Excellence; PBAC, Pharmaceutical Benefits Advisory Committee; PBM, pharmacy benefit management; PI, Pharmacoeconomics Initiative (in British Columbia, Canada); QALY, quality-adjusted life-year; TLV, Swedish Dental and Pharmaceutical Benefits Agency; US, United States.					

Contextual use of health economic evaluations

Macro level

There were large variations in the reported use of health economic evaluations among the macro-level decision makers. Systematic use of cost-effectiveness analysis was reported from the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia [27,28], the National Institute for Clinical Excellence (NICE) in England and Wales [15,36], and the Swedish Dental and Pharmaceutical Benefits Agency (TLV) [37,38]. In these reimbursement and clinical guidelines agencies, increased use of health economic evaluations was identified in situations with drugs with a large potential budget impact and when cost-effectiveness varied by indication and/or subgroups of patients. Based on observations of NICE's group deliberations, Williams et al. [36] reported that cost-effectiveness analysis in addition increased in importance when there were major disagreements among committee members regarding the value of the clinical evidence and when cost-effectiveness analysis helped decision makers to structure committee discussions and deliberations. Jansson [38] reported that the cost-effectiveness criterion was the major rationale for limiting or rejecting coverage by the TLV, which was suggested to be a result of a legislative demand for a transparent priority-setting process. Harris et al. [27] analyzed all submissions containing estimated cost per quality-adjusted life-year (QALY) or cost per life-year gained (LYG) and submitted to PBAC between 1994 and 2004. They found that those submissions that contained a cost per QALY were more likely to be used as last-line therapy than other submissions that were not QALY based. The use of economic modeling appeared to have only a small effect on the decisions to recommend coverage. In those cases in

which there was a strong political and/or public interest in the outcome of the process, the use of health economic evaluations seemed to decrease [35]. In addition, in cases of orphan drugs and in situations in which there was a lack of alternative therapies (particularly when the illness to be treated was severe), the use of a cost-effectiveness analysis was less commonly used [37].

In other settings, primarily the US and Canada but also some in European countries, health economic evaluations seem to be used more informally [23,26] or in a very limited scope [24]. Anell [39] notes, for example, that there was no evidence that the Pharmaceutical Price Board in Finland used health economic evaluations explicitly in the beginning of the 2000s, despite the Finnish requests for such data from manufacturers' submission since the early 2000s. This observation was explained by the lack of health economic competence in the Finnish committee, which has also been cited as an explanation of the lack of use of health economic evaluations in the French reimbursement system.

Meso level

There were few indications of meso-level decision makers using formal health economic evaluations as a basis for pharmaceutical priority setting. Rather researchers, for example, Späth et al. [34], highlight the relevance of price and budget impact in the meso health-care setting. According to Odedina et al. [30], the typical source of cost data is in-house hospital data (75%), published literature (57%), pharmaceutical industry studies (9%), and other (2%). A qualitative observational study of Swedish regional county council formulary committees pointed to the use of formal cost-effectiveness analyses in the initial two phases of the priority-setting process [17]. Most other

Table 2 – Summary of meso-level studies included in the review (chronological order).

Author(s) (year)	Settings	Methods	Factors/criteria/information	Use in context	Barriers
Sloan et al. (1997)	Managed care hospital pharmacy formulary in the US, hospital formulary decisions	Telephone survey (103 hospitals)	Reasons to add: high efficacy, low cost, doctor's request, easier dosing, better than existing drugs; reasons not to add: drug not reviewed, duplicate therapy or me-too drug, clinically inferior, high cost	Drug categories for which pharmacists had seen CEAs: gastrointestinal drugs, antibiotics, antithrombotic drugs, cardiovascular drugs, adjunct of coronary angioplasty, antiasthmatic drugs, nonsteroidal anti-inflammatory drugs	Too few studies, methodological issues (transferability), lack of health economic skills, studies published too late, industry bias, accessibility
Anell and Svarvar (2000)	Swedish county council formulary committee members, formulary decisions: regional treatment guidelines	Postal survey (216 respondents)	Therapeutic effects, cost-effectiveness, timely deliveries, number of years the drug has been on the market, and perceived reputation/credibility of the company	N/A	Lack of health economic skills, too few studies, methodological issues (transferability)
Kulsomboon et al. (2001)	Teaching hospitals in the US	Postal survey (166 respondents)	N/A	Developing treatment guidelines, requesting additional drug budgets or placing drugs on prior authorization; categories requiring CEAs: antiplatelet agents, systematic anti-infective drugs, and antineoplastic agents, glycoprotein IIb/IIIa inhibitors, cyclooxygenase II inhibitor, low-molecular weight heparin	Methodological issues (modeling), might expand if the US FDA review process incorporated approval of such data
Odedina et al. (2002)	Hospital formulary committee members (pharmacists) in the US (Florida)	Telephone survey (212 respondents)	Drug efficacy, drug toxicity, side effects, acquisition cost, costs weighted by benefits, extent of drug monitoring, availability of oral therapy, average hospital length of stay, in-house data, avoiding the use of home infusions	N/A	N/A
Martin et al. (2003)	Committees involved in hospital formularies in teaching hospitals in Canada (Toronto)	Document analysis (20 documents), interviews with key informants (18), and observation of group deliberations (3 P&T meetings)	Complex cluster of factors: efficacy, quality of evidence, safety (adverse effects and toxicity), number of patients, administration of the drug, hospital budget impact, prescribing restrictions, and informal cost-effectiveness	Highly contextual nature of the decision-making process; formal CEAs were seldom used, but cost data and informal cost comparisons were considered	Lack of studies, institutions (actors), process
Späth et al. (2003)	Pharmacists in hospitals (public-global budgets) and clinical departments (private, fee for service) in France (Rhône-Alpes region)	Qualitative interviews in 19 hospitals and clinical departments	Efficacy, safety, relations between decision makers and pharmaceutical industry, patient quality of life, economic criteria	Price and budget impact were more important in hospitals than in clinical departments; health economic evaluations were very rarely used	Lack of time and resources to collect and analyze data, lack of health economics competence, institutions (actors) and process (budgets, freedom of prescription), industry bias, methodological issues (transferability)

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Table 2 (continued)

Author(s) (year)	Settings	Methods	Factors/criteria/information	Use in context	Barriers
Jenkins and Barber (2004)	Drug and therapeutics committees in two general hospitals	Observation of group deliberations	Efficacy, cost (per dose, per unit of time, or total annual expenditure), pharmaceutical company activities, doctor's request, patient demand, pre-existing prescribing of a new drug, decisions of other DTCs, personality of the applicant	Increases in importance when relevant clinical trial data were equivocal or absent and low costs	N/A
Haslé-Pham et al. (2005)	Public hospital drug formulary committee members in France, Germany, The Netherlands, United Kingdom	Postal survey (143 doctors and 169 pharmacists)	Efficacy (88%), health economic analyses (78%), patient-reported outcomes (70%); most useful to have an expert in medicoeconomics (78%) at the hospital	French and German respondents used the results from health economic analyses less frequently than the English and Dutch respondents. Pharmacists and specialists were more frequently interested in CEAs than GPs.	Lack of health economic competence, methodological issues (transferability)
Williams and Bryan et al. (2007)	Trusts, county-wide priorities network, hospital medicine management committee, primary care area medicines management, interface medicines management committee	Postal survey (101 trusts), observation of committee meetings, documentary analysis, interviews	Efficacy, short-term cost, size of the clinical problem, scale of the potential investment, expected number of potential patients, implementation considerations, signature of budget holder	Health economic analyses were only requested in a small number of cases in primary and secondary care. Priorities networks made more use of health technology assessment and other research evidence. Other committees focused more on practical implementation issues of whether and how to restrict use and control prescribing.	Lack of health economic competence, accessibility of timely analyses, industry bias, inability to realize savings in practice, ethical considerations, methodological issues (variation in methodologies, robustness)
Chen et al. (2007)	Hospital medicine management committees (pharmacists), new drug applications (6)	Observation of committee meetings, interviews (10 interviewees)	Published reviews, efficacy, safety, acquisition cost, decisions made in other hospitals, doctor's request	Increased in importance when backing up the decisions that had already been made	Accessibility of timely analyses, lack of health economic competence, preference for cost-effectiveness data collected in clinical trials, methodological issues (transferability), lack of experience in searching for evidence in economic databases, industry bias, limited scope with regard to local budgets, presentation (aggregated)

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Table 2 (continued)

Author(s) (year)	Settings	Methods	Factors/criteria/information	Use in context	Barriers
Erntoft (2010)	County council formulary committee members in Sweden	Observation of committee meetings (n = 7), interviews	Medical appropriateness, medical tradition, health economics (cost-effectiveness), monetary consequences, elderly patients, new pharmaceuticals, administrative improvements, environmental concerns	Health economic evaluations were used in the two phases of the process; when preparing and during expert comments. When making decisions and launching the formulary, the health economics factor was defined as price.	Switches between scientific rationale and local rationale (practical issues), industry bias, lack of health economics competence
CEAs, cost-effectiveness analyses; FDA, Food and Drug Administration; GPs, general practitioners; N/A, not available; P&T, pharmacy and therapeutics; US, United States.					

studies investigating meso-level priority settings found less than stringent definitions of pharmacoeconomic data.

Similar to macro-level priority setting, the use of cost-effectiveness analyses increased if the potential budget impact was large, but also when there were new drugs that had recently been approved by reimbursement agencies. Examples of groups of drugs that fell into this category were antithrombotic drugs, cardiovascular drugs, antiasthmatic drugs [33], glycoprotein IIb/IIIa, cyclooxygenase II inhibitors, and low-molecular weight heparin [29]. Cost-effectiveness analysis has also been reported as a vehicle for motivating supplementary drug budgets or for placing drugs on prior authorization [29]. Based on observations of British Drug and Therapeutics Committees in two general hospitals, Jenkins and Barber [31] noted that the importance of costs increased when clinical trial data were ambiguous or absent. Another situation that spurred the use of cost-effectiveness analysis was the occurrence of a health economics-oriented national reimbursement agency. A survey among public hospital drug formulary committee members in France, Germany, The Netherlands, and the UK indicated that French and German respondents used the results of health economic evaluations less frequently than the English and Dutch respondents [40]. Cost-effectiveness has also proven to be useful to meso-level decision makers to support previous decisions [15].

Micro level

No identified article investigated the contextual use of health economic evaluations in local-level decision making. Jansson and Anell [21], however, were close by investigating the importance of costs in different settings. They found that there were three situations in which costs were relatively important: 1) when the physician had to choose between two or more generic drugs; 2) when the patient's illness or discomfort was of low priority (to the physician); and 3) when the patient did not request a specific drug.

Barriers to the use of health economic evaluations

Macro level

According to Hailey [35], a key to the successful use of economic analysis at PBAC has been the availability of a well-developed framework for evaluations linked to legislative provisions and clearly defined responsibilities within a government program. Harris et al. [27] note that political pressures, especially in cases of life-threatening conditions, have been the greatest threat to the Australian system. Based on the study of six macro-level decision-making bodies in Australia, Canada, Finland, the UK, and France, Anell [39] suggests that one major barrier to the explicit use of health economic evaluations was the lack of health economics

competence across committees. Both Cox et al. [41] and Grizzle et al. [42] note that decision makers find economic evaluations difficult to understand. Bryan et al. [36] argue that despite the extensive use of health economic evaluations by NICE, there was variability among committee members regarding the understanding of cost-effectiveness analysis. A number of additional issues related to the use of QALYs have also been identified in the NICE setting. Such examples are the lack of equity concerns in cost-effectiveness analyses, the preferences for disaggregated measures, and failure of QALYs as an outcome when it comes to incorporating issues of disease irreversibility or assessing benefits in situations of very severe conditions. In addition, problems such as difficulties in implementing threshold values and the lack of graphic presentations of models (presentational improvements needed) have been identified in the NICE setting. In managed care organizations (the US setting), a number of barriers have been reported including methodological issues (reliance on assumptions, lack of generalizability, discount rates, and concerns about the objectivity of firm-sponsored cost-effectiveness analyses) [23,24]. Key provincial respondents in a survey of five Canadian provinces stated concerns about missing data on a variety of issues such as effects of real-life costs and data associated with positive effects (e.g., fewer hospitalizations) [43]. Decision makers have also reported manufacturer provided models as unconvincing when it comes to estimating effectiveness in the Canadian setting.

Meso level

At the meso level, the most frequently mentioned barrier was the lack of applicability of cost-effectiveness analyses to hospital settings [14,16,33,34,40]. The lack of timely evaluations and the lack of time, resources, and competence to collect and analyze cost-effectiveness data were also perceived as considerable barriers in many studies. Other barriers reported in the meso-level health-care setting were skepticism toward modeling [29], closed budgets [34], a perceived bias in studies to the favor of the manufacturer, inability to realize savings in clinical practice, ethical objections and preferences for disaggregated measures instead of indices like QALYs [15], and switches between scientific and practical rationality (practical issues) [17].

Micro level

Only one of the five micro-level studies included in this review reported some form of evidence of barriers to the use of cost-effectiveness analyses. The study by Walley et al. [22] investigated British pharmaceutical advisors, indicating that there were differences regarding the perceived barriers to the use of health economic evalua-

Table 3 – Summary of micro level studies included in the review (chronological order).

Author(s) (year)	Settings	Methods	Factors/criteria	Use in context	Barriers
Brody et al. (1991)	Hospital physicians in the US: choice between two similar drugs (myocardial infarction)	Postal survey (2200 respondents)	Economic considerations WERE the main reason for their choice	Two different groups of physicians: cost-conscious group (less expensive and insufficient evidence to determine which drug is better) and the rationing group (there may be additional benefit, but insufficient to justify its extra cost)	N/A
Kangis and van der Geer (1996)	GPs and specialists in Greece: intention to prescribe	Survey (60 respondents)	Efficacy, safety, convenience, scientific evidence, trademark, goodwill, price (per pack, treatment vs. competition), reimbursement status	The intention of prescribing a pharmaceutical was significantly changed after viewing health economic evaluation	N/A
Walley et al. (1997)	Pharmaceutical advisors in England, Wales, and Scotland: prescribing advice	Postal survey (178 respondents)	Clinical issues, economic considerations	Actually discussed: drug acquisition cost and budgetary overspending. Would ideally like to discuss: cost-effectiveness from a societal perspective	Budget structures, industry bias
Erkan et al. (2002)	Specialists (rheumatologists) in the US: intention to prescribe	Postal survey (375 respondents)	Efficacy, cost-effectiveness	When cost is considered, physicians may limit their options for first-line treatment of RA; health economic analyses appear to play a dominant role in rheumatologists' choice of treatment regimens, at times contrary to the physician's perception of the effectiveness of a drug	N/A
Jansson and Anell (2006)	GPs and specialists in Sweden: intention to prescribe	Postal survey (738 respondents)	Efficacy, side effects, compliance, cost-effectiveness	N/A	N/A

GPs, general practitioners; N/A, not available; RA, rheumatoid arthritis; US, United States.

tions between prescribing physicians and pharmaceutical advisors. The major barriers, as perceived by the advisors, were the inflexibility of the existing National Healthcare System structures and a lack of credibility of the evaluations. In addition, a Swedish study [21] also investigated barriers, but the objective was rather cost considerations in general.

Discussion

Despite the fact that this review was not limited to location of literature, it is likely that the searches for literature have been inherently biased toward more recent publications and studies written in the

Table 4 – Overview of factors/criteria used in priority setting, contextual use of, and barriers to use of economic evaluations (macro, meso, and micro health-care levels).

Setting	Macro health-care level	Meso health-care level	Micro health-care level
Factors/criteria used in priority setting	Efficacy (clinical effectiveness), safety, cost-effectiveness	Efficacy (clinical effectiveness), safety, cost (cost-effectiveness, acquisition price, per treatment)	Efficacy (clinical effectiveness), safety, side effects, compliance, cost (cost-effectiveness, acquisition price, per treatment)
Contextual use of economic evaluations	Large budget impact, subgroups of patients, differences in interpreting clinical evidence, structuring process	Large budget impact, reimbursement agencies' interest in cost-effectiveness, request budgets, lack of clinical trial data, motivating decisions already made, preparation and expert comments	No relevant studies
Barriers to use of economic evaluations	Unconvincing modeling, lack of health economic skills, equity concerns, preference for disaggregated measures, unfavorable presentation, difficult to implement threshold values, implicit priority setting process	Mistrust of modeling, lack of HE skills, equity concerns, preference for disaggregated measures, manufacturer bias, lack of applicability to settings, lack of timely studies, rigid budget structures, unrealizable savings, scientific and local rationalities	Manufacturer bias, rigid budget structures

English language. Another limitation of the methodology is the lack of quantification of the results into a meta-analysis because of the problems of separating the local context from the use and hence the outcome. Instead, richer descriptions of studies are provided in place of quantifications of results. Yet another limitation is the single authorship of the review, which may have resulted in reviewer selection bias. To reduce this potential bias, the selection of articles to include in this review was supported by a senior researcher. Fortunately, there were no differences regarding the inclusion of studies, but in case of this situation, the author had access to a third senior researcher with decision power.

Study populations

With these limitations in mind, it is suggested that the study populations were clearly dominated by English-speaking countries such as the US, the UK, Canada, and Australia. Only a few more countries have been investigated regarding this subject, and all of these were European (Sweden, Finland, France, Germany, The Netherlands, and Greece). This review suggests that, to date, only three countries had investigated the use of health economic evaluations at all three health-care levels: the US, the UK, and Sweden.

Postal and telephone survey methods dominated ($n = 17$), followed by studies based on interviews ($n = 13$), document analysis ($n = 10$), and observation of group deliberations ($n = 9$). The methods used, however, were different at the three health-care levels. At the macro and meso levels, multiple methods were commonly used. At the micro level, postal survey was the only method used. Altogether, observation of group deliberations was the least used method. This may at least in part be explained as an access problem.

A majority (79%) of studies at the macro level were published between 2000 and 2008. The corresponding figures for meso- and micro-level decision makers were 92% and 40%, respectively. This indicates an increased (reported) use of economic evaluations in this setting during the past decade, at least at macro and meso levels.

Factors and criteria used in priority setting

This review suggests that efficacy and safety were the most important decision criteria used at all three health-care levels investigated (Table 4). The cost-effectiveness criterion was more important at a macro health-care level, whereas the reported use of the cost-effectiveness criterion was rather vague at meso and micro health-care levels. At these latter health-care levels, cost-effectiveness was defined in multiple ways (e.g., budget impact, informal cost-effectiveness, and cost per dose). These varied elements of costs considered in hospital and DTC priority setting have been confirmed by Walkom et al. [12]. One possible explanation may be the fact that there are few health economists practicing at those levels, and the knowledge of cost-effectiveness techniques consequently is scarce. These definitions may be seen as a second best alternative to cost-effectiveness or translations of the definition of cost-effectiveness, which are better suited to the institutional context. One example of this is the differences between physicians and pharmacists at the micro level in terms of the ranking of costs. Physicians ranked cost-effectiveness and price per pack next after patient compliance, whereas pharmaceutical advisors ranked acquisition costs and budget impact. In this case, both groups were reported to understand the concept of cost-effectiveness, but the incentive structure seemed to be different between physicians and pharmaceutical advisors. As noted by Vourenkoski et al. [13], use of subjective and value-based criteria has proved rational and legitimate in real-life priority setting.

Contextual use of health economic evaluations

Although most articles at the macro level contained some information regarding contextual use in terms of cases of decisions, this information was not available in any study at the micro level. Although decision makers at the macro level seemed to be rather orthodox in their use of health economic evaluations, meso-level decision makers seemed to be more

creative. For instance, Williams and Bryan [15] reported cost-effectiveness being used to legitimize decisions, which, in fact, had never been backed up by this kind of information. This may be connected with the reported increased use of cost-effectiveness analysis among public drug formulary members in countries with a health economics-oriented national reimbursement agency [40].

This review suggests further that the existence of explicit priority-setting processes increased the use of cost-effectiveness as both criterion and rationale, but also improved the structure of the decision-making process. The more informal use of health economic evaluations in North America (US and Canada) may be a consequence of a tradition of implicit priority-setting processes. A similar conclusion was made by Neumann [44] when exploring the use of cost-effectiveness analysis in the US. Other situations that increased the use of health economic evaluations were reimbursement and formulary decisions regarding pharmaceuticals with a large potential budget impact and subgroups of patients, when patient groups were lacking power or legitimacy to protest against priority-setting decisions, when high qualitative clinical trial data were missing, or when requesting additional budgets to finance the use of expensive pharmaceuticals.

Barriers to use of health economic evaluations

In a review of the general use of health economic evaluations, Edama and Coast [8] suggested that the barriers to use at the meso and micro levels can be divided into three categories: institutional and political factors (i.e., inflexibility of budgets and political objectives), cultural reasons (i.e., evidence of effectiveness more important than costs, individual patient vs. population perspective, lack of time and timeliness of economic evaluation), and methodological factors (i.e., assumptions in economic evaluations, lack of relevance). Most of these categories of barriers were also visible in pharmaceutical priority setting; however, there were differences between the health-care levels. Although meso- and micro-level decision makers reported shared barriers such as rigid budget structures, this did not seem to be a major problem at the macro level. This may be explained by the fact that some macro-level decision makers did not have responsibility for drug expenditures. This was a common feature among the macro-level decision makers that have reported use of health economic evaluations in this review: NICE, PBAC, and TLV. In addition, a study included in this review [40] found that the occurrence of health economic-oriented macro-level decision makers actually seemed to spur the interest in using health economic evaluations at the meso level. This suggests that there is a mimicking factor to consider in the use of health economic evaluations, i.e., decision makers adapt their decision making to other related institutions that are respected, thus legitimizing their own activities.

Political objectives have been suggested to decrease the use of health economic evaluations at the meso level [8]. The equity concern expressed by health-care decision makers at the macro and meso levels may be seen as a political barrier to the use of health economic evaluations. In addition, other cultural barriers such as the lack of (or the uneven distribution of) health economics skills to evaluate the models, discontentment with being provided aggregated measures, and a strong preference for disaggregated ones have been reported in this review. The preference for disaggregated measures may be explained by the incompatibility between the strategies normally used to reduce uncertainty in medical decision making and a calibrated measure such as QALYs [17]. Other cultural barriers at the meso level included issues such as unrealizable savings and lack of timely studies.

The remaining barriers identified in this review would probably correspond to methodological barriers. Interestingly, these barriers seem to be minor (in terms of number of mentioning; the conclusion drawn regarding the pattern identified was based on frequency of mentioning it as a barrier in the articles reviewed) compared with political and cul-

tural ones. Macro and meso health-care level decision makers, however, shared some similarities such as the mistrust of manufacturer-provided models, preference for health-care perspectives rather than societal perspectives, and lack of transferability of results to other settings.

Conclusion

This review investigates the factors and criteria used in pharmaceutical priority setting, the context-dependent use of health economic evaluations, and barriers to use at the macro, meso, and micro health-care levels. The cost-effectiveness criterion was MOST important TO macro-level decision makers, whereas the reported use of the cost-effectiveness criterion among meso- and micro-level health-care decision makers was rather vague. The barriers to the use of health economic evaluations had elements of institutional-political, cultural, and methodological issues. Factors that seem to support an increased use of health economics evaluations in pharmaceutical priority setting are well-developed frameworks for evaluations, the presence of health economics competence among decision makers, and explicit priority-setting processes. This review suggests that there are differences in how economic evaluations are used at the macro, meso, and micro levels, mainly because of differences in the rationale at each level. A suggestion for future research is to analyze two or all three health-care levels simultaneously to compare the uses. This is expected to increase the comparability of the use in different settings.

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